Supplementary Data

Predicted 3D structures for adenosine receptors bound to ligands:

Comparison to the crystal structure

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Docking of ZM241385 to the X-ray structure of $hAA_{2A}R$

As a validation of the docking techniques, we used GenMSCDock (next generation version of HierDock) to dock the antagonist, ZM241385, to the Exper* crystal structure of the $hAA_{2A}R$ (PDB ID: 3eml). In the crystal structure of $hAA_{2A}R$, seven waters surround the ligand in the binding site. We calculate that three of these have strong HBs with the two N atoms in the triazole cyclic ring and the terminal hydroxyl group in the phenyl ring (~ 1.8 Å H-bond distances, as shown in **Figure S1**), leading to 16% of the binding in the cavity analysis (**Table S1**). Of course, these waters are not present in our predicted structures.

Our best predicted structure (lowest cavity energy) is 1.06 Å RMSD from the xray structure (**Figure S2)**. The largest deviation was at the phenoxy ring exposed toward EL 2 and 3 due to the three waters surrounding the phenoxy ring in the X-ray complexes. Using an implicit water model, the total cavity energy is -43.79 kcal/mol for the X-ray structure and -44.55 kcal/mol for the GenMSCDock predicted structure.

We also used GenMSCDock to dock to the xray structure in which the waters are included explicitly. Here the lowest energy model is RMSD = 0.80 Å from the xray structure (**Figure S2)**.

Table S1. Cavity analysis (residue-ligand interaction energy in kcal/mol) of the x-ray complex of the A_{2A} adenosine receptor/ ZM241385 with explicit water in the "Exper*" column vs without explicit water in the "Exper* without water" column. Note that higher negative numbers indicate stronger binding. Energies stronger than -3 kcal/mol in dark blue, between -3 and -1 kcal/mol in blue, and between -1 and -0.5 kcal/mol in light blue.

Cavity		Exper*				Exper* without water			
Res.	#	VdW	Coulomb	H-Bond	Total NonBond	VdW	Coulomb	H-Bond	Total NonBond
ASN	253	4.58	-4.26	-8.89	-8.57	4.58	-4.27	-8.88	-8.58
GLU	169	0.56	-1.50	-5.85	-6.78	0.57	-1.50	-5.85	-6.78
PHE	168	-7.09	0.33	0.00	-6.76	-7.10	0.33	0.00	-6.77
LEU	249	-4.03	-0.20	0.00	-4.23	-4.03	-0.19	0.00	-4.23
WAT	772	4.00	-1.84	-5.13	-2.97	-	-	-	-
WAT	773	4.48	-2.07	-4.99	-2.59	-	-	-	-
MET	177	-2.01	-0.29	0.00	-2.30	-2.01	-0.29	0.00	-2.30
ILE	274	-2.24	-0.01	0.00	-2.26	-2.24	-0.01	0.00	-2.26
LEU	267	-1.99	-0.05	0.00	-2.04	-1.99	-0.05	0.00	-2.04
WAT	775	5.81	-3.11	-4.67	-1.97	-	-	-	-
TYR	271	-1.85	0.05	0.00	-1.80	-1.85	0.05	0.00	-1.80
HIS	250	-0.50	-0.87	0.00	-1.38	-0.51	-0.87	0.00	-1.38
LEU	85	-1.26	-0.05	0.00	-1.31	-1.26	-0.05	0.00	-1.31
MET	270	-1.57	0.33	0.00	-1.25	-1.57	0.32	0.00	-1.25
HIS	264	-1.15	0.06	0.00	-1.09	-1.15	0.06	0.00	-1.09
TRP	246	-1.04	0.04	0.00	-0.99	-1.04	0.04	0.00	-0.99
ASN	181	-0.53	-0.38	0.00	-0.91	-0.53	-0.38	0.00	-0.91
LEU	167	-1.07	0.24	0.00	-0.83	-1.07	0.24	0.00	-0.83
VAL	84	-0.58	-0.12	0.00	-0.70	-0.58	-0.12	0.00	-0.70
WAT	777	-0.23	-0.33	0.00	-0.56	-	-	-	-
ILE	66	-0.41	-0.14	0.00	-0.55	-0.41	-0.14	0.00	-0.55
WAT	776	-0.36	-0.04	0.00	-0.40	-	-	-	-
ILE	252	-0.30	-0.08	0.00	-0.38	-0.30	-0.08	0.00	-0.38
MET	174	-0.42	0.07	0.00	-0.35	-0.42	0.07	0.00	-0.35
THR	88	-0.32	-0.02	0.00	-0.34	-0.32	-0.02	0.00	-0.34
PHE	182	-0.18	-0.06	0.00	-0.24	-0.18	-0.06	0.00	-0.24
SER	67	-0.21	-0.02	0.00	-0.23	-0.21	-0.02	0.00	-0.23
ALA	265	-0.24	0.01	0.00	-0.23	-0.24	0.01	0.00	-0.23
THR	256	-0.16	-0.04	0.00	-0.20	-0.16	-0.04	0.00	-0.20
VAL	186	-0.10	0.01	0.00	-0.09	-0.10	0.01	0.00	-0.09
WAT	771	-0.27	0.21	0.00	-0.07	-	-	-	-
WAT	774	-0.29	0.29	0.00	-0.01	-	-	-	-
SUM					**-54.35**				**-45.81**

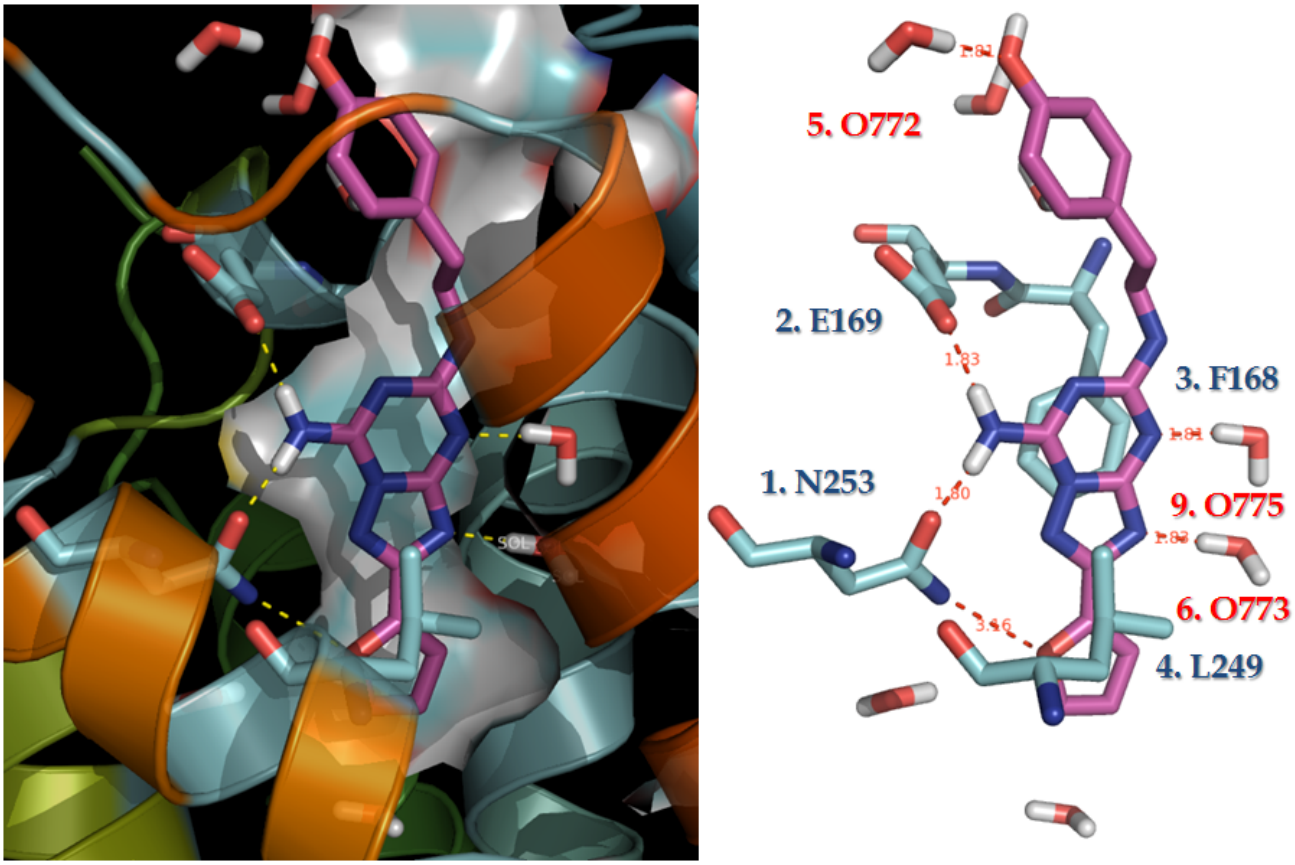

Figure S1. The binding site of ZM241385 for the Exper* x-ray structure of the A_{2A} adenosine receptor. Our docking model showed that E169 in the second extracellular loop and N253 in TM6 form H-bonds with the free amino group.

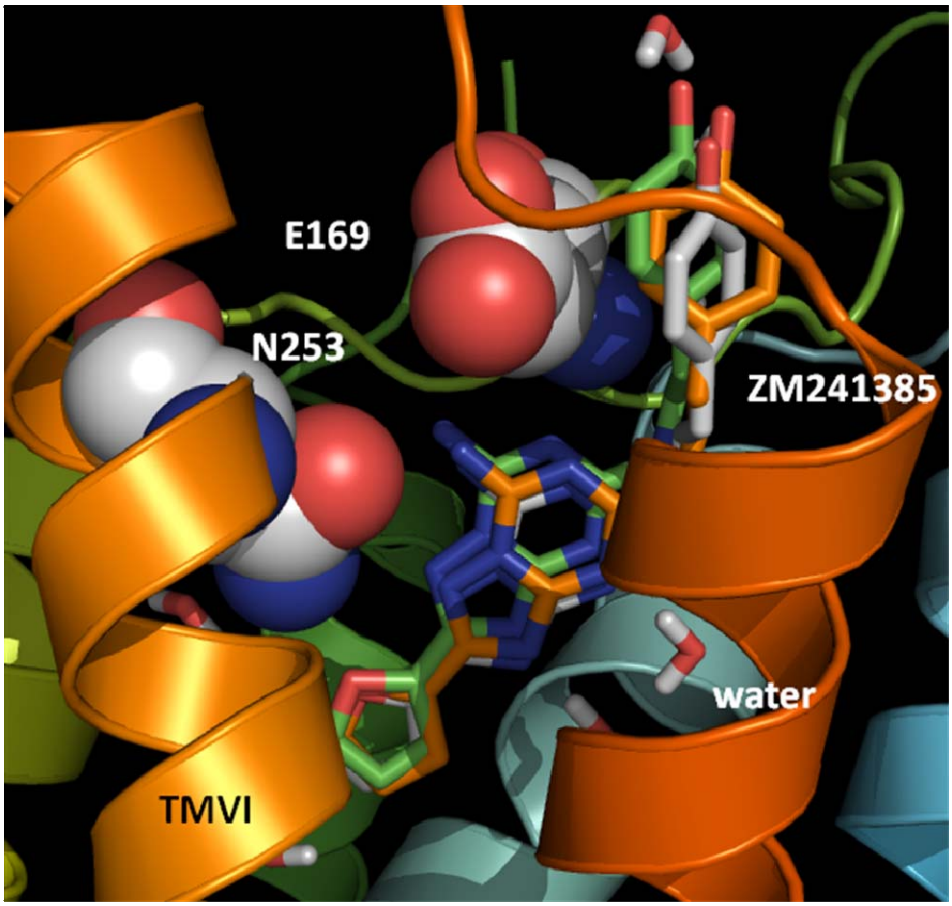

Figure S2. Superimposition of the predicted ZM241385 structure in green (implicit water model, 1.06 Å ligand RMSD) and orange (explicit water model, 0.8 Å ligand RMSD) with the crystal ZM241385 structure in white at the x-ray structure of the human A_{2A} adenosine receptor. E169 in the second extracellular loop and N253 (6.55) in TM6 form H-bonds with the exocyclic amino group.